

ADDENDUM TO PREVIOUS REVIEW

DATE: June 9, 2005

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SUBJECT: ODS Postmarketing Safety Review
Drug(s): Myzan (MT 100; naproxen/metoclopramide)
Sponsor: Pozen
NDA: 21-645
Further analysis of Tardive Dyskinesia cases

PID #: D050036

Upon review of the previous document outlining movement disorders associated with metoclopramide¹, concern was raised over the number of cases of tardive dyskinesia (TD) related to short term (<30 days) metoclopramide use. Further information was requested by the reviewing division regarding duration of therapy and outcome in these AERS cases. Although the proposed recommended dosing for Myzan (metoclopramide/naproxen) includes a limitation of 6 tablets per month (16 mg metoclopramide each), there exists a potential for off label dosing of the product. Migraine patients may exceed recommended dosing and it is feasible that use could approach one tablet daily in “chronic abusers” of migraine therapy. Information presented below provides the number and characteristics of AERS cases in which a short duration of therapy (<30 days) was associated with TD.

Figure 1 depicts the distribution of cases based on reported duration of therapy. The total number of cases reviewed for TD is 67.

¹ In DFS under NDA 21-645, author Mary Ross Southworth, June 7, 2005

Figure 1.

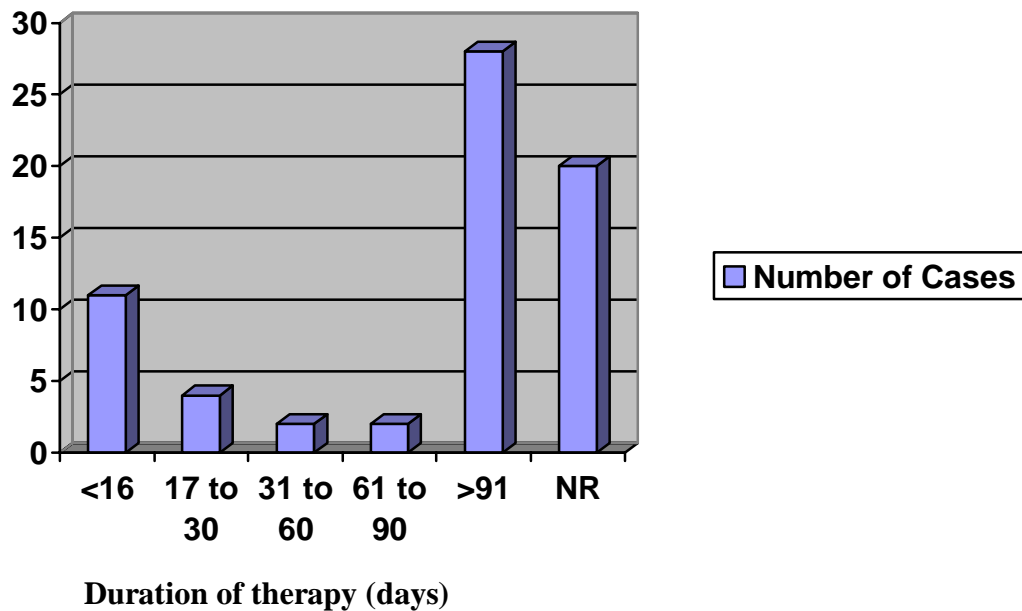


Table 1 describes pertinent details of each case in which duration of therapy with metoclopramide was 30 days or less. (NR=not reported)

Table 1. Characteristics of cases with duration of therapy <31 days (n=15)

Duration (days)	Route	Daily Dose	Concomitant med	TD symptom	Status of symptoms at time of reporting
0.5	IV/PO	NR/30	Promethazine	NR	Continuing
1	IV	40	None	Tremors	Continuing
1	PO	20	NR	Spasm; trismus	NR
1	IV	10	NR	Tongue rolling	NR
1	PO	40	None	NR	NR
2	PO	40	None	NR	Improved
3	PO	30	NR	Clenched hands	NR
4	PO	40	Amlodipine	Mouth movement	Continuing
7	IV	20	NR	NR	NR
15	PO	60	Risperidone	Lip smacking	NR

20	PO	40	Amlodipine	NR	Continuing
28	PO	NR	NR	NR	NR
30	PO	NR	NR	NR	NR
30	PO	40	NR	Lip smacking	Resolved
30	NR	20	Lithium	NR	NR

As noted in the original review, it is not possible to discern whether metoclopramide was taken intermittently or continuously for the duration of therapy listed based on the information provided in the AERS cases. Of the 15 cases presented, 5 cases listed a concomitant medication which has been associated with movement disorders.

Discussion: The majority of cases did not report whether symptoms of TD resolved after metoclopramide discontinuation. There were AERS cases in which short durations of therapy resulted in continuing (at the time of reporting) symptoms of TD. Five of 15 cases reported symptoms continuing (1 case reported symptoms as improved). Of these 5 cases, 2 cases involved some component of parenteral dosing. In the remaining 3, daily dose was reported to be 40 mg of oral metoclopramide (more than 2 times the metoclopramide contained in one tablet of Myzan).

Certainly, it is possible that an irreversible movement disorder may occur after very few doses of metoclopramide; however, there are very few AERS cases which report such a phenomenon.

Duration of therapy in Days

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/s/

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